Silver-catalyzed Annulation of Arynes with Nitriles for Synthesis of Structurally Diverse Quinazolines

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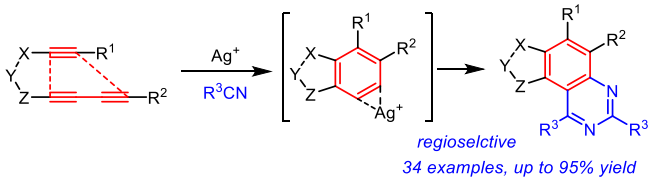
Supporting Information Placeholder



ABSTRACT: An efficient silver catalyzed-annulation reaction of aryne with nitriles to generate quinazolines is described. Arynes generated from triynes or tetraynes through hexadehydro Diels-Alder reaction (HDDA) readily participated in an [A+2B] mode of annulation with nitriles in the presence of $AgSbF_6$ catalyst. The mechanism was explored by DFT calculations, which supports the silver catalyzed formation of nitrilium ion as a key intermediate. This annulation generates an array of poly-substituted novel quinazoline derivatives with excellent regioselectivity.

Heterocyclic compounds draw significant attention of synthetic chemist because of its immense importance in human life.[1] Quinazoline, a family of nitrogen-based bicyclic aromatic compounds, constitutes the core of numerous biologically active molecules that show anticancer,[2a] antibacterial,[2b] antifungal,[2c] antiviral,[2d] antitubercular,[2e] anti-inflammatory,[2f] antimutagenic,[2g] anticoccidial,[2h] antimalarial,[2i] antileishmanial,[2j] antioxidants,[2k] neuroprotective,[2l] antiobesity,[2m] and antihypertensive activities.[2n] Prazosin,[3a] erlotinib,[3b] trimetrexate,[3c] vandetanib[3d] are representatives of marketed drugs (Figure 1)[3e-f]. Also, the unique photochromic behavior of quinazoline molecules[4] were exploited to elucidate cellular signaling processes of epidermal growth factor receptor (EGFR)[4c-d] and α_1-adrenergic receptors.[4e-f] Recently,

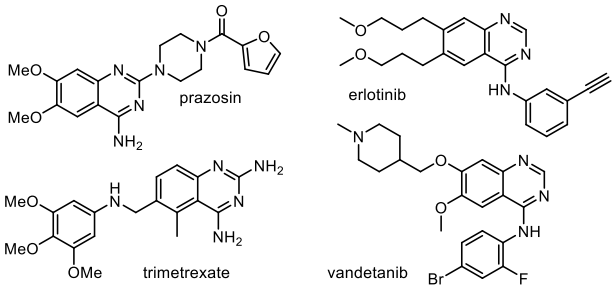
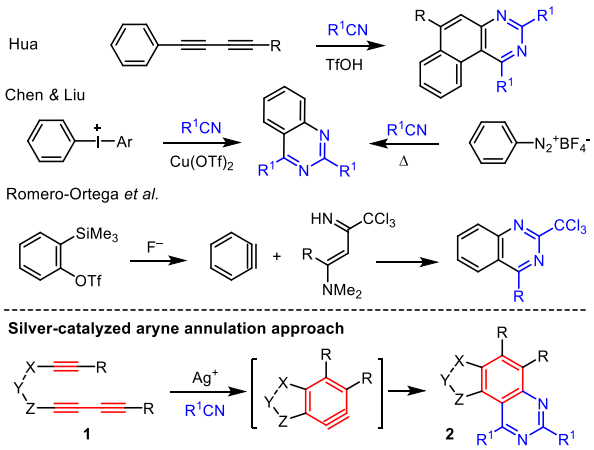


Figure 1. Representative quinazoline-based drugs

Scheme 1. [2+2+2] Annulation strategies for quinazoline synthesis



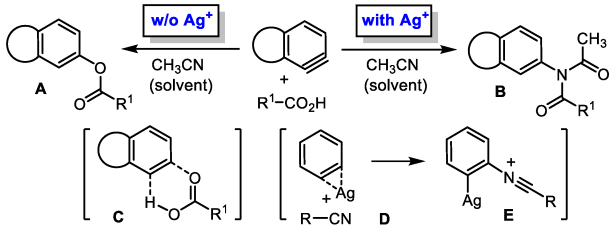
quinazolines are recognized as light-emitting materials for electronic devices.[5]

Many protocols for quinazoline synthesis via a nitrilium intermediate are reported in the literature,[6a-g] however, the generality of these methods is often limited by the requirement of pre-functionalized arene moieties. In theory, quinazolines can be generated via a formal [2+2+2] cycloaddition between alkyne or its functional equivalent and two molecules of nitrile[6a-e,6h-m] under thermal or acid-catalyzed conditions. Hua realized a

TfOH-catalyzed [2+2+2] cycloaddition reaction of 1,4-diaryl-1,3-butadiyne with nitriles to form quinazolines (Scheme 1).[6b] $Cu(OTf)_2$-mediated and thermal annulations are also developed to generate quinazolines by employing diaryliodonium[6c] or aryldiazonium salts.[6e] Although Romero-Ortega employed [4+2] cycloaddition of benzyne with 1,3-diazabutadiene derivatives to generate quinazolines,[7] however, direct annulation of benzynes with nitriles to form quinazolines has not been reported. In this regard, we envisaged a new double annulation strategy whereby tri- and tetrayne **1** is annulated to generate quinazolines **2** via in situ formation of an aryne followed by addition of two nitrile molecules catalyzed by a silver ion. A caveat in this approach is that the 1,3-diyne moiety in **1** should preferentially participate in hexadehydro Diels-Alder reaction[8] to generate an aryne intermediate before its engagement in other process. Herein we report successful implementation of an aryne-based [A+2B] type double annulation reactions for the synthesis of structurally diverse quinazoline derivatives.

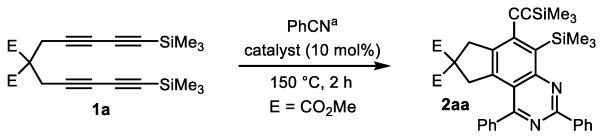
Silver catalysts are known to confer a profound impact on the reactivity of arynes.[9] By employing certain silver complexes as a catalyst, we have developed many aryne-based transformations including C–H insertion,[10] nucleophilic trapping,[11] hydroarylation,[12] hydrofluorination,[13] hydride transfer reaction,[14] and so forth[15]. It was shown that the reactivity preference of arynes toward different nucleophiles could be switched in the absence and presence of a silver catalyst. For example, the reaction of an aryne to generate aryl ester **A** from carboxylic acid in acetonitrile[16] could be completely redirected to provide *N*-arylimide **B** in the presence of a silver complex (Scheme 2).[11b] We surmised **A** is derived from a direct interaction of a more nucleophilic carboxylic acid with the aryne via **C**, whereas imide **B** results from the initial interaction of a silver-complexed aryne species with nitriles to form **D** followed by formation of a nitriliam intermediate **E**,[17] which is then trapped by a carboxylic acid.

Scheme 2. Differential reactivity of arynes in the absence and presence of silver catalyst



Based on these observations, we hypothesized that without a carboxylic acid, the putative intermediate **E** would be trapped with another molecule of nitrile, which will set for a favorable 6-*endo-dig* cyclization[18] of an organosilver moiety with the resulting nitrilium species to form quinazoline skeleton. With this hypothesis, we commenced our exploration with symmetric tetrayne **1a** and benzonitrile, and optimized the reaction conditions in terms of catalyst and temperature (Table 1). Among silver

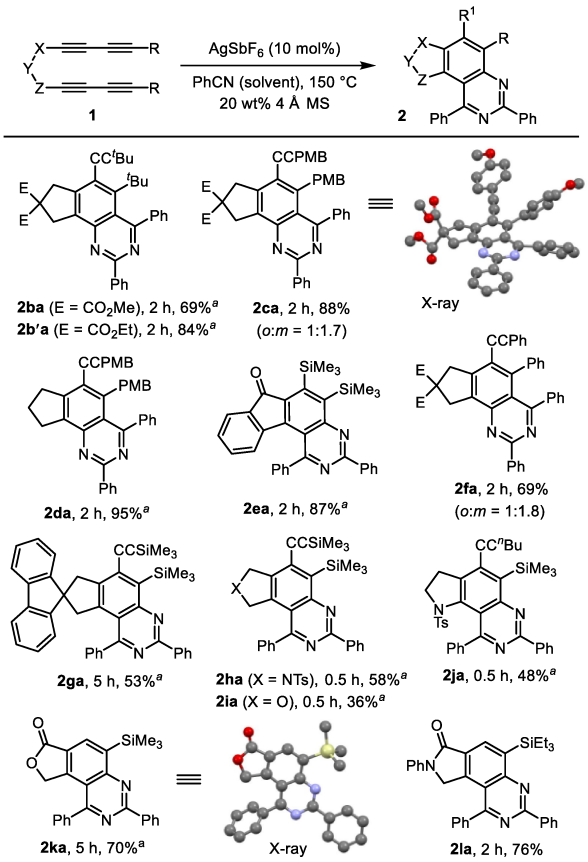
Table 1. Optimization of reaction conditions



entry	catalyst	yield (%)[b]	entry	catalyst	yield (%)[b]
1	AgOAc	5	7	$Mg(OTf)_2$	91
2	Ag_2CO_3	38	8	$In(OTf)_3$	2
3	AgOTf	47	9	$Sm(OTf)_3$	74
4	$AgSbF_6$	97[c]	10	AuCl	23
5	$AgSbF_6$	92[d]	11	$Cu(OTf)_2 \cdot C_6H_6$	34
6	$Zn(OTf)_2$	93	12	none	26

[a] Used as solvent. [b] NMR yields using an internal standard (1,5-difluoro-2,4-dinitrobenzene). [c] 92% yield at 120 °C after 12 h. [d] With 5 equiv PhCN.

Scheme 3. Quinazoline formation from arynes derived from structurally different tetraynes and triynes



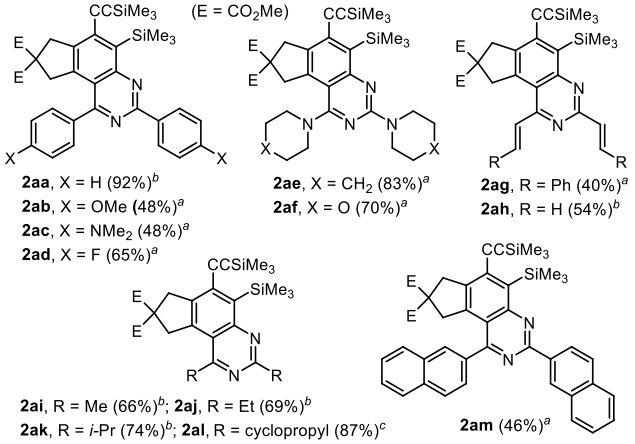
[a] 20 wt% 4 Å MS was added into reaction mixture.

complexes $AgSbF_6$ was found to be the most effective catalyst, while other metal triflates such as $Zn(OTf)_3$, $Mg(OTf)_2$, and salts, salts, $Sm(OTf)_3$ were also effective. With $AgSbF_6$ (10 mol %, 150 °C, 2 h) in benzonitrile as solvent, quinazoline **2aa** was obtained in 97% yield (entry 4). When the reaction was carried out in toluene with 5 equivalents of benzonitrile slightly lower yield (92%) was observed. It is noteworthy that a single isomer of **2aa** was generated from the reaction, which was unambiguously assigned by nOe experiments.

With the optimized conditions in hand, we next explored quinazoline formation from the aryne species derived from structurally different tetraynes (**1b–1d** and **1f–1j**)[19] and triynes (**1e**, **1k**, **1l**) (Scheme 3). While all carbon-tethered tetraynes are generally good substrate to generate quinazolines in high yield, nitrogen- and oxygen- tethered tetraynes afford somewhat low yield of the quinazolines.[20] There seems to be an inverse correlation between the rate of aryne formation and the yield of quinazoline. The aryne precursors forming arynes slowly (2 h) result in high yield of **2ba–2fa** in the range of 69–95%, except for **2ga** (5 h, 53%). On the other hand, the nitrogen- and oxygen-tethered tetraynes consumed quickly (0.5 h) tend to decompose to a larger extent, resulting in relatively lower yield of quinazolines **2ha–2ja** (36–58%). An ester-tethered triyne provided quinazoline **2ka** in 70% yield (5 h) while the corresponding amide-tethered triyne afforded **2la** in 76% yield (5 h). Substituents on aryne intermediates played a pivotal role for the regioselectivity of the first nitrile addition. Thus, *tert*-butyl group dictates the initial nitrile addition at the meta position from it (**2ba** & **2b′a**),[21] whereas with trimethylsilyl ($SiMe_3$) substituent,[22] nitrile addition selectively occurred at the ortho position (**2ea**), In case of aryl substituents, formation of a mixture of two isomers was observed with slight meta preference (**2ca** and **2fa**).[23] The identity of these isomers was unambiguously confirmed by X-ray diffraction analysis of **2ca** and **2ka**.[24]

Next, we examined annulation reactions of tetrayne **1a** with different nitriles (Scheme 4). In these reactions, the fluctuating yields with different substrates, most likely caused by adventitious water, became more consistent and improved by adding molecular sieve (4 Å, 20 wt%)[25] to the reaction medium. While the reaction with benzonitrile provided **2aa** in excellent yield (92%), with more electron-rich benzonitriles containing 4-OMe and 4-NMe_2 substituent, **2ab** and **2ac** were obtained in significantly lower yield (48%) and with 4-fluoro benzonitrile **2ad** was obtained in 68% yield. On the other hand, reactions with electron-rich aminonitriles such as piperidinecarbonitrile and 4-morpholinecarbonitrile afforded 2,4-diamino qunazolines[26] **2ae** and **2af** in 83 and 70% yield, respectively. Reactions of cinnamyl and vinyl substituted quinazolines cinnamylcarbonitrile and acrylonitrile (used as solvent) provided **2ag** and **2ah** in 40 and 54% yield. Aliphatic nitriles such as acetonitrile, propionitrile, isobutyronitrile, cyclopropane-carbonitrile provided quinazolines **2ai–2al**

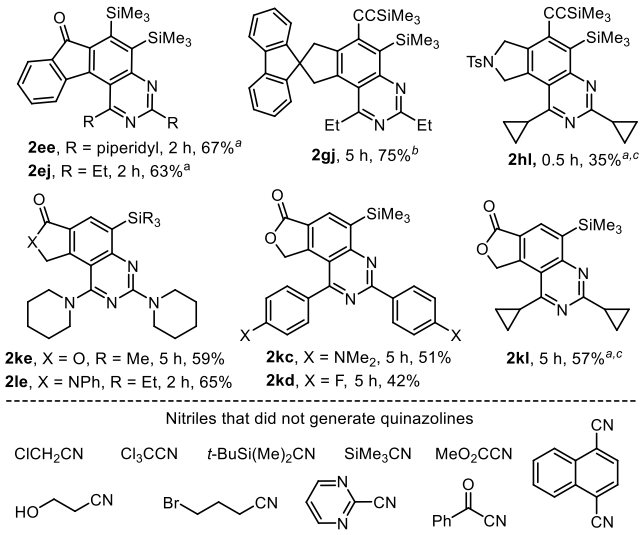
Scheme 4. Efficiency of quinazoline formation with tetrayne **1a** and different nitriles



Conditions: $AgSbF_6$ (10 mol%), toluene, 150 °C, 2 h. [a] With 5 equiv of nitrile. [b] Nitriles as solvent. [c] With 10 equiv of nitrile.

in good yield (66–87%) when employed as a solvent. Sterically more hindered naphthalene-2-carbonitrile (5 equiv) also provided quinazoline **2am** in moderate yield (46%). Subsequently, different combinations of aryne precursors and nitriles were employed to broaden the structural space of the quinazolines (Scheme 5). The reaction of ketoarene-tethered triyne generated **2ee** and **2ej** in 67 and 63% yield

Scheme 5. Quinazoline formation with structurally differentiated triynes and tetraynes with various nitriles



Conditions: $AgSbF_6$ (10 mol%), RCN (5 equiv), 150 °C. [a] With 20 wt% 4 Å MS. [b] Nitrile as a solvent instead. [c] With 10 equiv of nitrile.

within 2 h while a fluorene-tethered tetrayne generated **2gj** in 75% yield after 5 h. A heteroatom-tethered tetrayne provided **2hl** within 0.5 h in marginal yield (35%) regardless of the molecular sieve additive or an increased amount of nitrile. On the other hand, an ester- or an amide-tethered triynes provided 2,4-diamino-substituted quinazolines **2ke** (5 h, 59%) and **2le** (2 h, 65%). Also, quinazolines **2kc** (5 h, 51%), **2kd** (5 h, 42%), and **2kl** (5 h, 57%) were generated in slightly lower yields. In general, electro-neutral or electron-rich aliphatic and aromaticnitriles can participate in the reaction with arynes to furnish 2,4-disubstituted quinazoline derivatives in moderate to high yield. On the other hand, the reaction with electron-deficient nitriles or nitriles containing a sensitive functional group (see in the legend of Scheme 5) provided no or low yield of quinazoline products.

To gain further insight into the reaction mechanism and regioselectivity, we carried out DFT calculations[27] (SMD/M06/6-311++G(d,p)/SDD//B3LYP/631G*/Lanl2dz level of theory)[28] (Figure 2: Calculations employed an *N*Ts-tethered tetrayne (**1h**) that leads to product **2ha**). These calculated reaction profiles[27] indicate that silver complexed aryne (**IN1**) interacts with benzonitrile forms a more

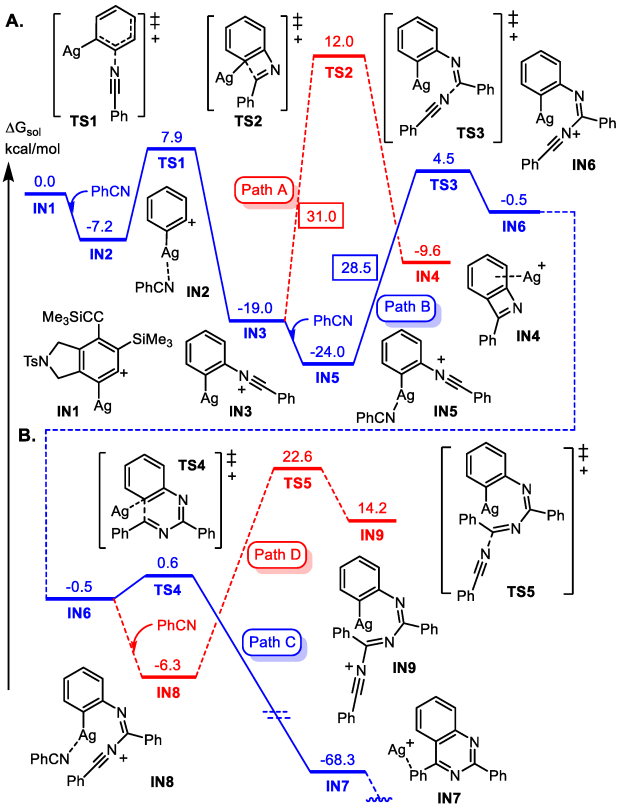


Figure 2. **A.** DFT-calculated reaction profiles for selective formation of intermediate **IN6** over **IN4** (**IN1** is the actual structure and the rest structures are abbreviated). **B.** Reaction profiles leading to quinazoline over triple nitrile adduct.

stable complex **IN2**, from which nitrilium species **IN3** could be formed via **TS1**. In the next step, intermediate **IN3** could undergo ring closure to generate azabicyclo **IN4**[29] in Path A but it requires high barrier (31 kcal/mol). On the other hand, **IN3** interacts with another benzonitrile to generate **IN5** exergonically in Path B. Due to a highly stabilized nature of an ionic complex **IN5**, its conversion to bis-nitrile adduct **IN6** via **TS3** requires an activation barrier of 28.5 kcal/mol, being 2.5 kcal/mol lower than the highest barrier in Path A.

Once intermediate **IN6** is generated in Path B, it can take two different reaction paths leading to ring closure or triple nitrile adduct formation (Figure 2B). The barrier for ring closure of **IN6** via **TS4** is only 1.1 kcal/mol (Path C), affording silver-complexed quinazoline **IN7**. On the other hand, the stabilized nitrile complex **IN8** formed from **IN6** in Path D should overcome a much higher barrier of 28.9 kcal/mol to proceed to the next intermediate **IN9**. Thus, the thermodynamically and kinetically favorable formation of **IN7** in Path C provides the observed quinazoline product **2ha**.

In summary, we have developed an efficient [A+2B] annulation of arynes with nitriles to form quinazolines under silver-catalyzed conditions. Structurally diverse and noble polysubstituted quinazolines could be synthesized by tuning the aryne precursors, structure and stoichiometry of nitriles, catalyst, temperature, and reaction time. Both tetraynes and electronically activated triynes readily undergo hexadehydro Diels-Alder reaction before other undesired reactions of the diyne moiety, thus serve as an effective platform for quinazoline formation. This double annulation process shows excellent regioselectivity, where a silyl group on the aryne intermediate plays a pivotal role to steer the initial addition of nitrile at its ortho position. In contrary, the reversed regioselectivity was observed with *t*-Bu substituted tetraynes, which is mainly due to unfavourable steric interaction between *t*-Bu and nitriles. DFT calculations provided important insight into the mechanism and selectivity for the formation of the observed quinazoline product from this silver catalyzed [A+2B] annulation reaction of arynes.

ASSOCIATED CONTENT

Supporting Information

The Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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